

Original Research Article

Assessment of thyroid function status in transfusion dependent thalassemic children

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Received: 29 November 2021

Revised: 29 December 2021

Accepted: 03 January 2022

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ABSTRACT

Background: Frequent blood transfusions have been associated with serum iron overload, which may result in hypothyroidism and other endocrine abnormalities in transfusion dependent thalassemic patients. Thyroid dysfunction has been reported in a number of studies on these pts. The aim of the study is to assess the thyroid function status among the transfusion dependent thalassemic children.

Methods: This was a cross sectional study conducted in the department of transfusion medicine, department of Pediatric hematology and oncology and department of hematology, Bangabandhu Sheikh Mujib medical university (BSMMU), Dhaka for a period of 18 months. A total number of 86 children with transfusion dependent thalassemia who met the inclusion and exclusion criteria were studied. Demographic data as well as history of blood transfusion and chelation therapy were collected. Thyroid function and iron load status were evaluated by measuring serum FT₄, TSH and ferritin levels.

Results: Out of 86 thalassemia patients, euthyroid patients were 77 (89.5%) and hypothyroid patients were 9 (10.5%). Eight (9.3%) patients were compensated and 1 (1.2%) was uncompensated hypothyroidism. Statistically significant association was found between number of blood transfusion and serum ferritin level (≥ 2000 ng/ml) with development of hypothyroidism in thalassemic patients. Mean ferritin level was higher in hypothyroid (4797.8 ± 2027.4 ng/ml) group than in euthyroid (3628.8 ± 2448.5 ng/ml) groups.

Conclusions: Frequency of hypothyroidism was 10.5% (compensated 9.3% and uncompensated 1.2%). Number of blood transfusion and ferritin level were found significantly associated with the development of hypothyroidism in thalassemic patients.

Keywords: Thyroid function, Transfusion dependent, Thalassemia

INTRODUCTION

Thyroid hormones are critical determinants of brain and somatic development in infants and of metabolic activity in children; affecting the function of virtually every organ. Thyroid dysfunction has been reported in a

number of studies on thalassemia patients.¹ Transfusion dependent thalassemia pts require regular blood transfusion to survive. Without adequate transfusion support, they would suffer several complications and a short life span. This category includes patients with β -thalassemia major and severe HbE β -thalassemia.²

A world health organization report has shown that 3% of population carries β -thalassemia and 4% carries Hb E in Bangladesh.³ Khan et al estimated that existing thalassemia patient in Bangladesh is about 1 lac and suspected total number of β -thalassemia major and Hb E β -thalassemia born around 1040 and 6443 per year respectively in the country.⁴

The basic defect in β thalassemia is a reduced or absent production of β globin chains with relative excess of α chains. The direct consequences are a net decrease of hemoglobin production and an imbalance of the globin chain synthesis.⁵ The most common combination of beta-thalassemia with abnormal Hb or structural Hb variant with thalassemic properties is HbE/beta thalassemia which is most prevalent in Southeast Asia.⁴

Frequent blood transfusions, iron overload, poor compliance to therapy and chronicity of the disease contributed to a whole spectrum of complications including cardiac problems, hypogonadism, diabetes mellitus, hypothyroidism, hypoparathyroidism and other endocrine and metabolic problems in adolescents and young adults suffering from transfusion dependent thalassemia.⁶

Hypothyroidism is the second most common endocrine disorder after hypogonadism. The majority of patients have subclinical or mild forms, while approximately one-third has the overt form. Central hypothyroidism is less frequent. Regular assessment of FT₄ and TSH is recommended in thalassemia patients after the first decade of life.^{7,8} The frequency of hypothyroidism in Thalassemia patients ranges from 6 to 30% in different studies.^{6,9} Several studies found that incidence of hypothyroidism was not related to high level of serum ferritin level.¹⁰⁻¹² Other studies showed significant higher level of serum ferritin levels in hypothyroid group as compared to euthyroid group.^{13,14}

Very few studies are available from Bangladesh to determine the thyroid function status in thalassemia patients. One study was done by Karim et al found hypothyroidism was present in 10 (20%) patients. Among these, compensated (subclinical) hypothyroidism was in 5 (10%) cases and decompensated (overt) hypothyroidism was 5 (10%) cases.¹⁵

The aim of the study is to determine the thyroid function status in transfusion dependent thalassemic children that may create awareness among the pediatricians about the necessity for evaluation of thyroid function in these patients.

METHODS

Type of study

Cross-sectional observational study type was used in the study.

Place of study

Study conducted at department of transfusion medicine, BSMMU and department of pediatric hematology and oncology, BSMMU and department of hematology, BSMMU

Period of study

The study carried out from February 2018 to August 2019.

Selection criteria

Inclusion criteria

Patients diagnosed as transfusion dependent thalassemia (Beta thalassemia and Hb E/ beta thalassemia), age ranged from 5-18 years and received at least 10 times of blood transfusion were included in the study.

Exclusion criteria

Patients who received less than 10 times of blood transfusion, very ill and known case of hypothyroidism were excluded from the study.

Ethical approval

Ethical clearance was taken from institutional review board (IRB) of BSMMU. The patients and their parents were informed about the study design and its objectives. They were explained that there will be no physical or social risk for the participants other than the regular activity as done for admitted cases. They were also informed about freedom to participate or not to participate at any time. No incentive was given for participation. Informed written consent was taken. All the information remained confidential.

Statistical analysis

All data was recorded systematically in preformed data collection form. The entered data was checked, verified and analyzed by appropriate computer software. Statistical analysis was performed by using SPSS, version 21. Data were expressed as frequency, percentage, mean, standard deviation, median and range. The data was presented in tabular form. Appropriate statistical test was applied for data analysis. Categorical variables were compared by chi-squared test or Fischer's exact test. Unpaired t test was used to compare between two variables. Correlation was done by using Pearson correlation co-efficient. P value less than 0.05 was considered statistically significant.

Eighty-six patients diagnosed by Hb electrophoresis fulfilling the inclusion criteria were taken as study group. Age of the patients were 5-18 years. Age, gender, type of

thalassemia, age of first diagnosis and first transfusion, total number of transfusions, type and duration of iron chelation therapy, adherence to iron chelation therapy, and family history of thalassemia and thyroid disorder were recorded. Height and weight of the children were measured in standard procedure. 4 ml of venous blood was drawn aseptically on the morning of attendance for regular blood transfusion of thalassemic children. Serum free thyroxine (FT4), thyroid stimulating hormone (TSH) level and serum ferritin level were estimated by chemiluminescent immunoassay using the access Beckman Coulter analyser in the laboratory of microbiology department of BSMMU. On the basis of their thyroid profile the thalassemic patients were further divided into euthyroid, compensated hypothyroid and uncompensated hypothyroid.

RESULTS

The study included 86 patients of transfusion dependent thalassemia. Among them 21 (24.42%) were beta thalassemia major and 65 (75.58%) were Hb E beta thalassemia. Total male was 51 (59.3%) and female were 35 (40.7%). Mean weight and height were 31.73 (± 10.48) kg and 130.2 (± 15.2) cm respectively. Median weight for age Z score and median height for age Z score were -1.89 (-0.82 to -4.07) and -2.95 (-0.86 to -4.96) respectively. Mean BMI was 18.3 (± 3.40) kg/m². The mean age at first diagnosis was 17.3 (± 7.65) months, mean age at first blood transfusion was 19.21 (± 7.58) months, mean total duration of disease was 10.99 (± 4.05) years, and mean total number of blood transfusion was 82.6 (± 32.2) units. History of thalassemia in other family members was found in 23 patients (26.74%) (Table 1).

Among the thalassemic patients, the 70.93% received iron chelation therapy. Forty-three (70.5%) patients took oral deferiprone and 8 (13.1%) took deferasirox. Combination of deferiprone and deferoxamine were taken by 2 (3.3%) patients and combination of deferiprone and deferasirox were taken by 8 (13.1%) patients. Twenty-one (24.4%) patients had good compliance to iron chelation therapy. The mean duration of taking iron chelation therapy was the 17.93 (± 15.52) months (Table 1).

Euthyroid patients were 77 (89.5%) and hypothyroid patients were 9 (10.5%). Among hypothyroid patients 8 (9.3%) patients were compensated and 1 (1.2%) was uncompensated hypothyroidism (Table 2).

Significant association was found between higher serum ferritin level (≥ 2000 ng/ml) and hypothyroidism in thalassemia patients ($p < 0.05$) (Table 3).

No significant difference found in terms of mean age, sex, weight, height, WAZ score, HAZ score between euthyroid and hypothyroid cases. There was no significant difference in terms of age at first diagnosis (months), total duration of disease (years), age at first

blood transfusion (months), number of cases received iron chelation therapy, duration of iron chelation therapy in months and number of cases with good compliance to iron chelation therapy between the two groups. Hypothyroid patients received significantly greater number of blood transfusions than euthyroid patients ($p < 0.0001$) (Table 4).

Table 1: Demographic and clinical characteristics of study population. (n=86).

Variables	Patients (%)
Age (mean\pmSD) (years)*	12.52 \pm 3.96
Sex**	
Female	35 (40.7)
Male	51 (59.3)
Weight (Mean \pm SD) (kg)*	31.73 \pm 10.48
Height (Mean \pm SD) (cm)*	130.2 \pm 15.2
WAZ median (range) °	-1.89 (-0.82 to -4.07)
HAZ median (range) °	-2.95 (-0.86 to -4.96)
BMI (Mean \pm SD) (kg/m²) *	18.3 \pm 3.40
Type of thalassemia**	
β thalassemia major	21 (24.42)
Hb E β thalassemia	65 (75.58)
Age at first diagnosis (Months)*	17.3 \pm 7.65
Total duration of disease (Years)*	10.99 \pm 4.05
Age at first blood transfusion (Months)*	19.21 \pm 7.58
Total number of transfusions*	82.6 \pm 32.2
Number of cases having affected family member**	23 (26.74)
Number of cases received iron chelation therapy*	61 (70.93)
Type of iron chelation therapy*	
Deferiprone	43 (70.5)
Deferasirox	8 (13.1)
Deferiprone + Deferoxamine	2 (3.3)
Deferiprone + Deferasirox	8 (13.1)
Number of cases had good compliance to iron chelation*	21 (24.4)
Duration of iron chelation therapy in months**	17.93 \pm 15.52

*Values of quantitative data were presented as mean (standard deviation), **Values of qualitative data were presented as number (percentage), °HAZ and WAZ score were presented as median (range).

Table 2: Thyroid function status in study population.

Thyroid function status	N	Percentage (%)
Euthyroid	77	89.5
Hypothyroid		
Compensated	8	9.3
Uncompensated	1	1.2
Total	86	100

Table 3: Serum ferritin levels.

Serum ferritin (ng/dl)	Euthyroid, (n=77) (%)	Hypothyroid, (n=9) (%)	P value
≥2000	49 (63.6)	9 (100)	0.028 ^s
<2000	28 (36.4)	0 (0)	

Table 4: Comparison of demographic and clinical characteristics between euthyroid and hypothyroid cases in thalassemia patients.

Variables	Euthyroid, (n=77) (%)	Hypothyroid, (n=9) (%)	P value
Age (Years)	12.28±3.95	13.89±3.48	0.246 ^{ns*}
Sex			
Female	46 (59.7)	5 (55.6)	1.00 ^{ns**}
Male	31 (40.3)	4 (44.4)	
Weight (kg) (Mean ± SD)	31.39±10.6	34.67±9.51	0.378 ^{ns*}
Height (cm) (Mean ± SD)	129.9±15.48	132.7±13.13	0.617 ^{ns*}
WAZ	-2.03±0.78	-2.23±1.01	0.483 ^{ns*}
HAZ	-2.76±1.06	-3.40±0.81	0.083 ^{ns*}
Age at first diagnosis (months)	17.22±7.73	18±7.35	0.774 ^{ns*}
Total duration of disease (years)	10.75±4.03	13.05±3.86	0.108 ^{ns*}
Age at first blood transfusion (months)	19.12±7.84	20±5.2	0.744 ^{ns*}
Total no. of transfusions	77.5±27.3	126.1±39.4	<0.0001 ^{s*}
No. of cases received iron chelation therapy	55 (71.43)	6 (66.66%)	0.766 ^{ns**}
Duration of iron chelation therapy in months	18.7±15.87	11.33±10.58	0.179 ^{ns*}
No. of cases with good adherence to iron chelation therapy	28 (36.36)	1 (11.11)	0.129 ^{ns**}

*P value reached from unpaired t test, **p value reached from fisher exact test, ns=not significant, s=significant.

The mean ferritin level was higher in hypothyroid (4797.8±2027.4 ng/ml) group than in euthyroid (3628.8±2448.5 ng/ml) group but p value was not significant. Mean FT₄ and TSH values were significantly

different in euthyroid and hypothyroid groups (p≤0.0001) (Table 5).

Table 5: Mean values of ferritin, FT₄ and TSH in euthyroid and hypothyroid patients.

Mean values	Euthyroid, (n=77)	Hypothyroid, (n=9)	P value
Ferritin (ng/ml)	3628.8 (±2448.5)	4797.8 (±2027.4)	0.172 ^{ns}
FT₄ (ng/dl)	1.215 (±0.041)	1.036 (±0.246)	<0.0001 ^s
TSH (μIU/ml)	2.791 (±1.266)	7.951 (±1.597)	<0.0001 ^s

P value reached from unpaired t test, s=significant, ns=not significant.

DISCUSSION

Thyroid dysfunction has been reported in a number of studies on thalassemia patients. Given the varying data on thyroid function status in thalassemia patients, it is important to evaluate thyroid function status of them in our country. Such information may help in the determination and appropriate management of hypothyroid cases among the transfusion dependent thalassemic children.

In the present study, mean age of the studied patients was 12.52 (±3.96) years consistent with the study done by Jain et al where mean age was 10.3±3.6 years.¹⁶ Among 86 patients, 21 (24.42%) were beta thalassemia major and 65 (75.58%) were Hb E beta thalassemia, similar to the study done by Tahura et al where HbE-β Thalassemia was found the commonest type of thalassemia among Bangladeshi children.¹⁷ In the present study, the majority (70.93%) received iron chelation therapy. Only 21 (24.4%) patients had good compliance to iron chelation therapy. The mean duration of taking iron chelation therapy was 17.93 (±15.52) months. In our study, thalassemia patients had poor adherence to iron chelation therapy which is similar to study done by Al-Kloub et al.¹⁸ So, the findings may suggest that clinician should be aware of high prevalence of low adherence to chelation therapy in thalassemia patients.

In the present study, among 86 patients with transfusion dependent thalassemia, 9 cases (10.5%) were hypothyroidism. Eight cases (9.3%) were compensated and only one case (1.2%) was decompensated hypothyroidism. Kurtoglu et al found 12.8% hypothyroidism cases in transfusion dependent thalassemia patients in Turkey which was consistent with the present study.¹⁹ Somchit et al reported 17.6% hypothyroid cases in thalassemia patients.²⁰ A study done by Karim AKMR et al showed 20% patients with hypothyroidism, which was higher than the present study.¹⁵ Another study done by Sharmin et al in thalassemia patients of Bangladesh and 26% of their studied children had subclinical hypothyroidism which

was also higher than the present study.²¹ This wide variation in the frequency of hypothyroidism has been attributed to several factors such as patients' genotype, age, ethnic groups, and differences in treatment protocols of transfusion and chelation with marked variations in compliance and efficiency.^{22,23}

In the present study, compensated hypothyroidism (88.9%) was prevalent among the hypothyroid patients which was consistent with the studies done by Sharmin et al, Zervas et al, Farmaki and Agarwal et al.²²⁻²⁵ Uncompensated hypothyroidism was only 11.1% among the hypothyroid patients in the present study, which was similar to the study done by Gathwala et al as they found 12% uncompensated hypothyroidism.²⁶

In our study, all hypothyroid cases had ferritin level of ≥ 2000 ng/ml and a significant association between hypothyroidism and high ferritin level (≥ 2000 ng/ml) was found ($p=0.028$). This finding was consistent with the study done by Hantrakool as they suggested elevated serum ferritin level is a predictor of the development of hypothyroidism in thalassemia patients with iron overload and the maximum serum ferritin levels of greater than $3,500 \mu\text{g/dl}$ are associated with hypothyroidism in their study.²⁷ These findings may necessitate the value of iron chelating therapy to maintain serum ferritin levels below 2000 ng/ml and this may delay or avoid the development of hypothyroidism in patients with thalassemia.

The mean age of patient with hypothyroidism in this study was $13.89 (\pm 3.48)$ years, which was consistent with the study done by Somchit et al, Princiglioglu et al, Hashemi et al and Malik et al who suggested that complications of iron overload don't appear until the 2nd decade of life.^{13,20,23,28}

Sanctis et al suggested that Thyroid dysfunction usually starts in the second decade, and increases gradually in the third and fourth decades of life in patients who started early chelation therapy. In patients starting late iron chelation therapy, or with poor compliance to treatment, dysfunction of thyroid starts earlier. Therefore, an assessment of thyroid function is generally recommended after the age of 10 years.²⁹

Jain et al and Jehanzeb et al observed that no statistically significant difference between euthyroid and hypothyroid groups in terms of age and sex as present study.¹⁶ But total number of transfusions has statistically significant difference between euthyroid and hypothyroid groups ($p \leq 0.0001$) in present study which was consistent to the study done by Neha et al.³⁰ This finding suggests hypothyroidism is related to the iron overload due to increased number of blood transfusion.

In the present study, there was no statistically significant difference in terms of chelation therapy, duration of chelation therapy or its compliance between the euthyroid

and hypothyroid groups in thalassemic patients which is consistent with the study done by Upadya et al.³¹ Probable explanation may be hypothyroidism may develop due to some other factors besides iron overload such as chronic hypoxia in thalassemic patients.

Limitations

The limitations of the study were-small sample size, study depict picture of single centre tertiary care hospital. It may not be the picture of the whole thalassemic population in our country and thyroid autoantibody and serum ferritin level should have been studied in all hypothyroid cases as it may be associated with autoimmune thyroiditis or low iodine level which was not done in the present study.

CONCLUSION

In the present study we documented hypothyroidism in transfusion dependent thalassemic children. Among them majority were compensated hypothyroidism. Higher number of blood transfusion and ferritin level ≥ 2000 ng/dl was found significantly associated with the development of hypothyroidism in thalassemic patients.

ACKNOWLEDGEMENTS

Author would like to thanks to honorable teacher and guide professor, department of pediatrics, BSMMU whose direct supervision helped me to complete my thesis. Also, to thank all the teachers, my colleagues, students and nurses of hematology and Pediatrics ward who helped me in various ways in this study. Finally, would like to pay my regards to all those patients without whom this study would not be possible.

Funding: Funding sources by University thesis grant, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee of IRB Board of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.

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Cite this article as: Mazumder ABMOH, Begum S, Parvin R, Akter S, Shanta SA. Assessment of thyroid function status in transfusion dependent thalassemic children. *Int J Contemp Pediatr* 2022;9:146-51.